

The University of North Carolina and the American Chemistry Council Collaborated to Organize a Workshop

**FORMALDEHYDE SCIENCE INVITED EXPERTS WORKSHOP
UNDERSTANDING POTENTIAL HUMAN HEALTH CANCER RISK – FROM DATA
INTEGRATION TO RISK EVALUATION**

October 10 – 11, 2017

Location: UNC Friday Center, 100 Friday Center Drive, Chapel Hill, NC 27599

Co-Chairs: Drs. James Swenberg and Kenneth Mundt

Points for the discussions today:

- ❖ Background about formaldehyde
- ❖ The current risk assessment landscape
- ❖ The meeting itself – goal, invitees, session structure, topics
- ❖ Overview of some of the conclusions/recommendations from the meeting
- ❖ Recommendations for integrating data streams into a formaldehyde risk evaluation

Some Background about Formaldehyde

- ☐ At concentrations above 6 ppm in rats, where there is clear cytotoxicity and cell replication, it causes nasal cancer in rats.
- ☐ One of the most extensively studied chemical carcinogens
- ☐ Present in all cells at an appreciable level - tenths of mmoles/liter
- ☐ Estimated background exhaled concentrations of several ppb
- ☐ Endogenous formaldehyde-DNA reaction products have a high background
- ☐ Inconsistent epidemiology in occupational cohorts
- ☐ Risk assessments across the world are highly divergent

A View of the Risk Assessment Landscape

ORGANIZATION	POPULATION	APPROACH	RISK LEVEL	Basis of Decision
EU/ECHA	General	Qualitative but not low-dose linear	No convincing evidence of a carcinogenic effect at distant sites	Causes tumors above a threshold concentration by mechanisms that are initiated by the cytotoxic effects but ...data does not allow firm conclusion on a threshold-mode of action"
Health Canada	General	Threshold Carcinogen DSL Low priority substance	2.3×10^{-10} at 1 ppb	Carcinogenic hazard to humans "...under conditions that induce cytotoxicity and sustained regenerative cell proliferation."
Occupational Standards from various bodies in the US and EU	Workers	Threshold Carcinogen	Exposure standards: TWAs with STELs 0.1 ppm ACGIH; 0.016 pp NIOSH; 3ppm MAK and SCOEL	Varied: from MAK - Cancer classification 4: non-genotoxic; cell proliferation important to MoA to ACGIH's "cancer classification A1: confirmed human carcinogen "
NTP Report on Carcinogens (2011)		Qualitative	Known human carcinogen	Sufficient evidence in humans for nasal tumors and myeloid leukemia
IARC Monographs 10F (2010)		Qualitative	Known human carcinogen	Sufficient evidence in humans for tumors at both sites
IRIS (2010)	General	Low dose linear	1×10^{-4} at 1 ppb	For NPC, mutagenic MoA operating in conjunction with key event of formaldehyde cytotoxicity-induced cell proliferation; sufficient evidence of causal association for NPC and LHP cancer in humans

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With ongoing work on a new IRIS assessment, it was considered an opportune time to bring together highly-regarded, subject matter experts and discuss how diverse data streams could be brought together to conduct an up-to-date risk evaluation

Formaldehyde Science Invited Experts Workshop Attendee List

Name	Affiliation	Email
Bruce Rodan	Environmental Protection Agency	Bruce.Rodan@epa.gov
Chap Thompson	ToxStrategies, Inc.	chapthompson@toxstrategies.com
David Coggen	University of Southampton	d.coggen@soton.ac.uk
Emilio Pira	University of Turin	emilio.pira@unit.it
Erin Dickson	American Chemistry Council	erin.dickson@accchem.org
Gray Marsh	University of Pittsburgh	graymarsh@pitt.edu
Harvey Checkoway	University of California San Diego	hcheckoway@ucsd.edu
Harvey Clewell	ScitoValon/Ramboll Environ	hclewell@scitovalon.com
Hertz-Peterson	Consultant to Formacare	hertzpeterson@formacare.com
Hélmut Greim	Independent Consultant	greim.helmut@t-online.de
Hermann Bolt	Independent Consultant	h.bolt@t-online.de
Iris Camacho	Environmental Protection Agency	Iris.Camacho@epa.gov
Jim Bus	Exponent	jim.bus@exponent.com
Jim Sherman	Celanese	jeremy.sherman@celanese.com
Jim Swenberg	University of North Carolina	jswenber@unc.edu
Kenneth Mundt	Ramboll Environ	kenneth.mundt@ramboll.com
Kimberly White	American Chemistry Council	kimberly.white@accchem.org
Kris Thayer	Environmental Protection Agency	kthayer@epa.gov
Mark Graumwald	Hexion	mark.graumwald@hexcel.com
Mel Andersen	ScitoValon	mel.andersen@scitovalon.com
Michael Thirman	University of Chicago	mthirman@uchicago.edu
Paulo Boiteira	Johns Hopkins School of Medicine at Mount Sinai	paulo.boiteira@mountsinai.org
Raj Sharma	Georgia-Pacific	raj.sharma@gp.com
Robina Gentry	Ramboll Environ	rgentry@ramboll.com
Rory Conolly	Environmental Protection Agency	Rory.Conolly@epa.gov
Sam Cohen	University of Nebraska Medical Center	scohen@unmc.edu
Stewart Holm	American Forest & Paper Association	stewart.holm@afpa.org
Sue McMillan	Oregon Department of Environmental Quality	sue.mcmillan@deq.or.gov
Tom Starr	TDS Associates	tom.starr@tdsassoc.com

Four regulatory scientist – Bruce Rodan, Kris Thayer, Iris Camacho and Sue McMillan – and one EPA scientist from NHEEL – Rory Conolly.

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TUESDAY, OCTOBER 10, 2017	
Time	Item
8:30am – 9:00am	REGISTRATION (UNC Friday Center – Main Vestibule and Dining Areas)
9:00am – 9:05am	WELCOME AND LOGISTICS – Kimberly White and Jim Swenberg (5 minutes)
9:05am – 9:10am	Workshop Purpose and Objectives – Ken Mundt (5 minutes)
9:10am – 9:25am	Understanding the Formaldehyde Science and Putting the Puzzle Pieces Together – Integrating New Science into Risk Evaluation Processes – Rebecca Gentry (15 minutes)
9:25am – 9:40am	Summary of Global Risk Assessment Approaches for the Formaldehyde Science – General Approaches in EU, Canada, WHO and the US – Jim Ben (15 minutes)
9:40am – 10:00am	SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE INTO POSSIBLE CARCINOGENICITY AND POTENTIAL FOR CAUSALITY (Chair: James Swenberg)
9:40am – 10:00am	European Approach for Evaluating the Formaldehyde Science: OEL, Nasal Impacts and Threshold Assessment – Hermann Bolt (20 minutes)
10:00am – 10:20am	Formaldehyde and Nasal Carcinogenesis: What Does the Epidemiology and Animal Data Tell Us? – Gary Marsh (20 minutes)
10:20am – 12:00pm	Discussion – Key Views by Participants on Charge Questions and MOA Framework: • Charge Question #1 Discussion (25 minutes) • Charge Question #2 Discussion (25 minutes) • Charge Question #3 Discussion (25 minutes) • Open Discussion (25 minutes)
12:00pm – 1:00pm	LUNCH (UNC Friday Center – Main Vestibule and Dining Areas)
1:00pm – 1:05pm	SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE INTO THE CANCER AND POTENTIAL FOR CAUSALITY (Chair: Ken Mundt)
1:05pm – 1:25pm	Key Events and Considerations for LBP Cancers – Ken Mundt (20 minutes)
1:25pm – 1:45pm	Overview: Epidemiology Evidence – Harvey Checkovsky (20 minutes)
1:45pm – 2:05pm	Overview of the Animal Science – Chad Thompson (20 minutes)
2:05pm – 2:25pm	LBP Cancers and Biological Plausibility – Can Exposure Formaldehyde Reach the Bone Marrow? Jim Swenberg (20 minutes)
2:25pm – 3:45pm	Discussion – Key Views by Participants on Charge Questions and MOA Framework: • Charge Question #4 Discussion (25 minutes) • Charge Question #5 Discussion (25 minutes) • Charge Question #6 Discussion (25 minutes) • Open Discussion (25 minutes)
3:45pm – 4:00pm	BRFAR (UNC Friday Center – Main Vestibule and Dining Areas)
4:00pm – 4:15pm	Looking Across Data Streams to Draw Conclusions Regarding Causality: Key Considerations in the Formaldehyde Science Survey Covered (15 minutes)

4:15pm – 5:30pm	Discussion – Key Views by Participants on Charge Questions: • Charge Question #7 Discussion (30 minutes) • Charge Question #8 Discussion (30 minutes) • Open Discussion (15 minutes)
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5:30pm	ABHORN DAY 1 OF WORKSHOP
6:30pm – 8:00pm	DINER – OFFSITE (Location TBD)

WEDNESDAY, OCTOBER 11, 2017	
Time	Item
8:30am – 9:00am	REGISTRATION (UNC Friday Center – Main Vestibule and Dining Areas)
9:00am – 9:05am	REGISTRATION (UNC Friday Center – Main Vestibule and Dining Areas)
9:05am – 9:10am	SESSION 3: FORMALDEHYDE – DATA RICH CHEMICAL RIFE FOR RISK EVALUATION? (Chair: Jim Swenberg)
9:00am – 9:25am	Overview of State-of-the-Science Approaches for Data Integration – Kimberly White (15 minutes)
9:15 – 9:30am	Recap of Day 1 Discussions: Identified Data Gaps and Uncertainties – Information Needs for a Formaldehyde Risk Evaluation Met Andersen (15 minutes)
9:30am – 11:45am	Discussion – Key Views by Participants on Charge Questions: • Charge Question #9 Discussion (20 minutes) • Charge Question #10 Discussion (30 minutes) • Charge Question #11 Discussion (30 minutes) • Charge Question #12 Discussion (20 minutes) • Charge Question #13 Discussion (30 minutes) • Open Discussion (15 minutes)
11:45am – 12:00pm	Workshop Wrap and Next Steps
12:00pm	LUNCH (UNC Friday Center – Main Vestibule and Dining Areas)
1:00pm	ABHORN DAY 2 OF WORKSHOP

SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY

1. Does the available scientific evidence support a specific MOA and causal association with NPC?
 - o What mechanistic evidence is available to support the proposed modes of action frameworks discussed for NPC? What are the uncertainties?

Suggested Discussants for Charge Question: Mel Andersen, Herman Bolt, Harvey Clewell, Rory Conolly, Gary Marsh
2. What are the key animal data for characterizing the shape of the dose-response curve for formaldehyde-induced nasal tumors? What are the key epidemiological studies for formaldehyde-induced nasal tumors and how would you reconcile differences between these studies?
 - o If a causal association can be established for human, what exposure metrics are associated with evidence of carcinogenicity? Is there evidence of a threshold for NPC in humans?

Suggested Discussants for Charge Question: Mel Andersen, Herman Bolt, Harvey Clewell, Rory Conolly, Peter Gelboke, Helmut Greim, Gary Marsh
3. What quantitative methods (e.g., linear and non-linear low dose extrapolation, threshold, PBPK modeling for dose-response assessment) would best characterize the potential for NPC risk in humans?
 - o Are there uncertainties with any of these quantitative methods that suggest this type of modeling should not be applied?

Suggested Discussants for Charge Question: Harvey Clewell, Rory Conolly, Roberto Geary, Tom Starr

SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY

4. What does the totality of the animal and epidemiology evidence tell us about the potential for a causal association with LHP and what conclusions can be drawn?
 - o What role does endogenous production play in drawing conclusions regarding LHP?
 - o Do the available data support a specific mode of action for hematopoietic cancers?

Suggested Discussants for Charge Question: Paolo Boffetta, Harvey Checkoway, David Coggon, Sam Cohen, Roberto Geary, Joseph Haney, Enrico Piza, Jim Swenberg, Michael Therman, Chad Thompson
5. What mechanistic data are critical to understanding a causal association between formaldehyde exposure and specific hematopoietic cancers?

Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg, Michael Therman
6. Do epidemiology studies provide useful dose response data for LHP?

Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg, Michael Therman
7. What methods for assessing causality and evidence integration are best applied to the available data for LHP cancer for conducting a hazard assessment (e.g., Bradford Hill criteria, biological systems approach, hypothesis based weight of evidence framework, systematic review, combination of approaches)?

Suggested Discussants for Charge Question: Mel Andersen, Paolo Boffetta, Harvey Checkoway, David Coggon, Ken Mundt, Enrico Piza, Kris Thayer
8. What uncertainties are important for consideration when integrating the available evidence? **Suggested Discussants for Charge Question:** Mel Andersen, Sam Ewis, Harvey Clewell, Sam Cohen, Roberto Geary, Tom Starr

SESSION 3- FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION?

9. What should be considered as the problem formulation and questions to be addressed when conducting a formaldehyde risk evaluation?
10. What are the best available approaches to conduct a robust evaluation of formaldehyde carcinogenic potential?
11. How can the approaches used to evaluate and integrate scientific evidence inform the risk assessment?
 - o What aspects of the Biological Systems Approach can be used to integrate the formaldehyde data?
 - o How can hypothesis based weight of evidence approach be to integrate the data streams for determinations of causality?
12. What needs to be added or changed in the draft IPCS Mode of Action Framework: nasal carcinogenicity?
13. What is the comparative weight of evidence for each hypothesized mode of action for nasal carcinogenicity?

Suggested Discussions for All Charge Questions – All Participants

Today, we want to convey a sense of the discussions, conclusions and recommendations from the group for the path forward

- I. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys and their implications for responses to formaldehyde beyond the front of the nose.
- II. Dr. Mundt – key recent epidemiological evaluations related to NPC, AML and Mode of Action
- III. Dr. Andersen – recommendation for integrating the rodent and human studies into a more quantitative risk evaluation for formaldehyde.

II. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys

Formaldehyde-Induced DNA-Protein Crosslinks

- DNA-Protein Crosslinks (DPCs) have long been known to be genotoxic.
- Heck and Casanova conducted extensive studies on rats and primates exposed to radiolabeled formaldehyde.
- We have now developed a chemical-specific method for the dG-OHMe-cysteine DPC that can measure both endogenous and exogenous DPC.

Time to Steady-State for Exogenous [$^{13}\text{CD}_2$]-HO-CH₂-dG Adducts in Nasal Epithelium

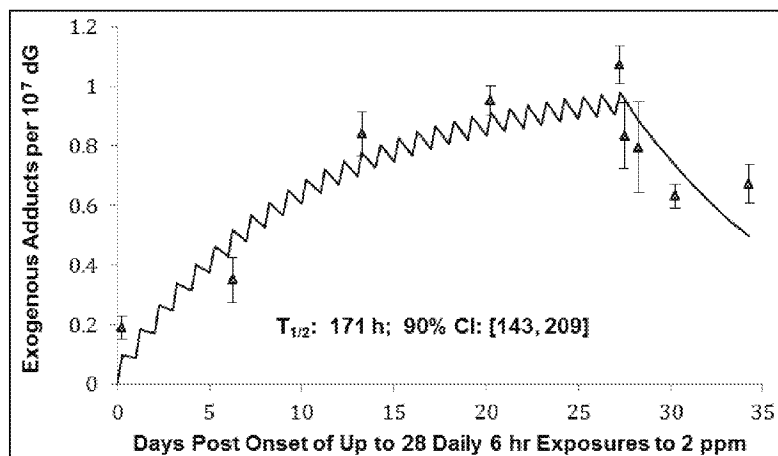
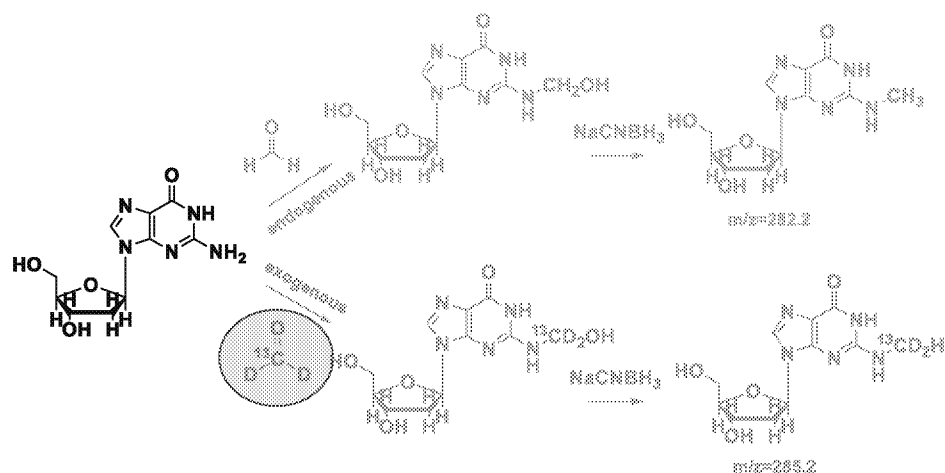
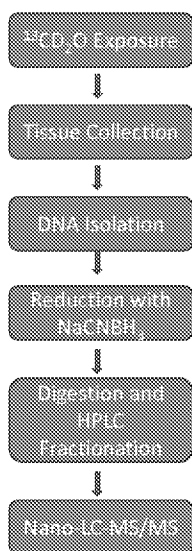


Figure 4. Estimated time for exogenous [$^{13}\text{CD}_2$]-*N*²-HOME-dG adducts to reach the steady-state concentration and $t_{1/2}$ of exogenous [$^{13}\text{CD}_2$]-*N*²-HOME-dG adducts following a 2-ppm {6h/day} exposure for 28 days [Observed (mean \pm sd) and predicted (solid line)].

Looking at *Adducts* originating from both endogenous and exogenous formaldehyde.

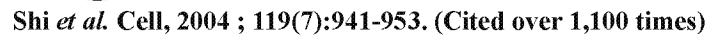


Formation of N^2 -HOMe-dG mono-adducts (mean \pm SD) in rat nasal epithelium, bone marrow and white blood cells exposed to 2-ppm labeled formaldehyde for 28 days.

Exposure period	Rat nasal epithelium			Rat bone marrow			Rat white blood cells		
	N^2 -HOMe-dG (adducts/ 10^7 dG)			N^2 -HOMe-dG (adducts/ 10^7 dG)			N^2 -HOMe-dG (adducts/ 10^7 dG)		
	Endogenous ^a	Exogenous	n	Endogenous ^a	Exogenous	n	Endogenous ^a	Exogenous	n
7 days	2.51 \pm 0.63	0.35 \pm 0.17	5	3.37 \pm 1.56	n.d.	6	2.62 \pm 1.12	n.d.	4
14 days	3.09 \pm 0.98	0.84 \pm 0.17	5	2.72 \pm 1.36	n.d.	6	2.26 \pm 0.46	n.d.	4
21 days	3.34 \pm 1.06	0.95 \pm 0.11	5	2.44 \pm 0.96	n.d.	6	2.40 \pm 0.47	n.d.	4
28 days	2.82 \pm 0.76	1.05 \pm 0.16	6	3.43 \pm 2.20	0.34 ^b	12	2.49 \pm 0.50	n.d.	4
28 days + 6h post expo	2.80 \pm 0.58	0.83 \pm 0.33	9	2.41 \pm 1.14	n.d.	6	2.97 \pm 0.58	n.d.	4
28 days + 24h post expo	2.98 \pm 0.70	0.80 \pm 0.46	9	4.67 \pm 1.84	n.d.	5	2.57 \pm 0.58	n.d.	4
28 days + 72h post expo	2.99 \pm 0.63	0.63 \pm 0.12	9	5.55 \pm 0.76	n.d.	6	1.75 \pm 0.26	n.d.	4
28 days + 168h post expo	2.78 \pm 0.48	0.67 \pm 0.20	10	2.78 \pm 1.94	n.d.	4	2.61 \pm 1.22	n.d.	4
Air control	2.84 \pm 0.54	n.d.	8	3.58 \pm 0.99	n.d.	6	2.76 \pm 0.66	n.d.	6

^a No statistically significant difference was found using the two-sided Dunnett's test (multiple comparisons with a control) (Dunnett, 1964). ^b The amount of exogenous N^2 -HOMe-dG adducts that was found in only one bone marrow sample analyzed by AB SCIEX Triple Quad 6500. n.d. = not detected.

A Postulated pathway for Demethylation of diMeK4H3 by LSD1



dG-Me-Cys in Rats Exposed to High Levels of Formaldehyde

Rats Exposed to 15 ppm

Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of rats exposed to 15 ppm of formaldehyde (6 h per day)

Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10 ⁶ dG)	
		Endogenous	Exogenous
Nose	0	6.50 ± 0.30 (n=5)	ND*
	1	4.42 ± 1.10 (n=6)	5.52 ± 0.80
	2	4.28 ± 2.34 (n=6)	4.69 ± 1.76
	4	3.67 ± 0.80 (n=6)	18.18 ± 7.23
PBMC	0	4.98 ± 0.61 (n=5)	ND
	1	3.26 ± 0.73 (n=4)	ND
	2	3.00 ± 0.98 (n=5)	ND
	4	7.19 ± 1.73 (n=5)	ND
Bone Marrow	0	1.49 ± 0.43 (n=3)	ND
	1	1.67 ± 0.18 (n=3)	ND
	2	1.66 ± 0.57 (n=3)	ND
	4	1.41 ± 0.21 (n=3)	ND

* ND, Not detected

Similar responses are seen in Primates

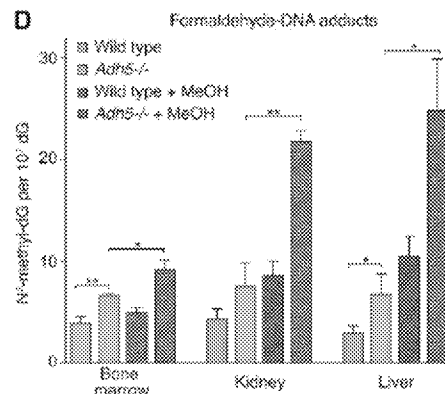
Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of primates exposed to 6 ppm of formaldehyde (6 h per day)

Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10 ⁸ dG)	
		Endogenous	Exogenous
Nose	0	3.59 ± 1.01 (n=5)	ND
	2	3.76 ± 1.50 (n=5)	1.36 ± 0.20
PBMC	0	1.34 ± 0.25 (n=5)	ND
	2	1.57 ± 0.58 (n=4)	ND
Bone Marrow	0	2.30 ± 0.30 (n=4)	ND
	2	1.40 ± 0.46 (n=5)	ND
Liver	0	15.46 ± 1.98 (n=6)	ND
	2	11.80 ± 2.21 (n=6)	ND

* ND, Not detected

Formaldehyde derived DNA reaction products in various tissues from formaldehyde precursors

- ☐ A variety of compounds are metabolized to formaldehyde – e.g., methanol, caffeine, aspartame, many drugs.
- ☐ Tissue formaldehyde adducts are found after with dosing mice methanol.
- ☐ With formaldehyde, no DNA-adducts are found at sites other than in the front of the nose in either rats or the non-human primates.
- ☐ **Inhaled formaldehyde does not reach these other tissues**



Pontel *et al.* Molecular Cell, 2015; 60(1):177-188

Ongoing Studies on Formaldehyde DNA-reaction products

- Low dose exposures in rats (air control, 1 ppb, 30 ppb, 300 ppb)
- Breath analysis shows approximately 1-2 ppb in humans
- 1 ppb is approximately the same as breath analysis with no exposure to formaldehyde
- Expected completion of mass spectrometry by January 2018

II. Key New Epidemiological Evidence/Analyses: NPC, AML and Mode of Action – Dr. Kenneth Mundt

- Marsh et al. (2014, 2016) challenge conclusion of NPC association as “neither consistent with the available data nor with other research findings”
 - “driven heavily by anomalous findings in one study plant (Plant 1)”
 - Nasal/sinus cancers seemed more plausible than NPC, but increased risk not seen.
- Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009)
 - Separated myeloid leukemias into acute (AMLs) and chronic (CML)
 - Associations seen with Hodgkin lymphoma and CML, but not observed in other studies
 - Evaluated associations with “peak” exposure
- Gentry et al. (2013) and Mundt et al. (2017) reanalysis of Zhang et al. (2010) demonstrate no association between formaldehyde exposure and any reported outcome among exposed workers.

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No excess mortality from AML or CML observed

	Checkoway et al. 2015				Beane Freeman et al. 2009			
	Non-exposed (n=3,136)		Exposed (n=22,483)		Non-exposed (n=3,108)		Exposed (n=22,511)	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Myeloid leukemia	4	0.69 (0.19-1.76)	44*	0.86 (0.64-1.16)	4	0.65 (0.35-1.74)	44	0.90 (0.67-1.21)
AML	4	0.93 (0.25-2.37)	30	0.80 (0.56-1.14)	NR		NR	
CML	0		13	0.97 (0.56-1.67)	NR		NR	

US mortality rates used as the reference

*One death was coded to ICD-8 205.9, unspecified myeloid leukemia.

Association between peak exposure and mortality using most specific diagnosis (Checkoway et al. 2015)

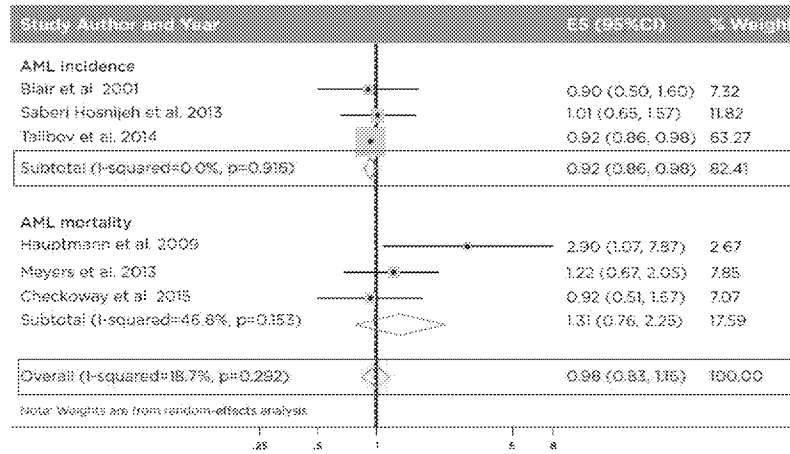
Diagnosis	No peak		≥2.0 to < 4.0 ppm		≥4.0 ppm		P trend
	Obs	HR (95% CI)	Obs	HR (95% CI)	Obs	HR (95% CI)	
Hodgkin lymphoma	15	1.0 (referent)	5	2.18 (0.77-6.19)	7	3.38 (1.30-8.81)	0.01
Myeloid leukemia	27	1.0 (referent)	11	2.09 (1.03-4.26)	10	1.80 (0.85-3.79)	0.06
AML	21	1.0 (referent)	7	1.71 (0.72-4.07)	6	1.43 (0.56-3.63)	0.31
CML	6	1.0 (referent)	3	2.62 (0.64-10.66)	4	3.07 (0.83-11.40)	0.07

Of 13 AML deaths with peak >2.0 ppm, only 4 had any peak within the 20 years of death; **only 1 AML death occurred (similar to expected) within 2 to 15 years** (typical latency window).

Uncertain relevance of exposure measure – predicted peak exposure – with no measures of actual exposures

No increased risk of AML is seen in relation to occupational exposure to formaldehyde

AML studies stratified by incidence vs. mortality



More complete analysis of Zhang et al. 2010 data

- Zhang et al. (2010) reported significant “changes”^{*} in blood parameters and aneuploidy in in vitro cell cultures.
- Concluded, “formaldehyde exposure can have an adverse effect on the hematopoietic system and that **leukemia induction by formaldehyde is biologically plausible**, which heightens concerns about its leukemogenic potential from occupational and environmental exposures.”

^{*}Study was cross-sectional and reported differences in blood parameters between exposed and unexposed workers were measured at one point in time; no changes were investigated over times (boldface emphasis added).

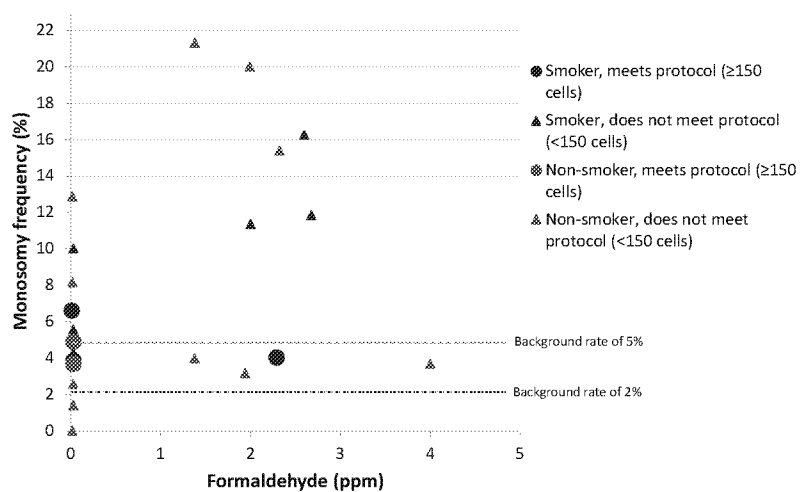
Association between formaldehyde exposure and WBC and RBC counts and components do not show expected dose-response

Exposure	<u>Blood Count</u> Adjusted RR	95% CI	†p-value	<u>Blood Count</u> Adjusted RR	95% CI	†p-value
<u>WBC</u>						
Unexposed	1.00			<u>RBC</u>		
<1.3 ppm	*0.87	0.78-0.97	0.943	*0.94	0.91-0.98	0.947
≥1.3 ppm	*0.85	0.76-0.96		*0.94	0.90-0.98	
<u>Lymphocytes</u>						
Unexposed	1.00			<u>Hemoglobin</u>		
<1.3 ppm	*0.85	0.75-0.96	0.660	0.98	0.94-1.01	0.818
≥1.3 ppm	*0.79	0.69-0.90		0.99	0.95-1.03	
<u>Monocytes</u>						
Unexposed	1.00			<u>MCV</u>		
<1.3 ppm	0.90	0.77-1.06	0.973	1.03	0.99-1.08	0.550
≥1.3 ppm	0.89	0.75-1.04		1.06	1.02-1.11	
<u>Granulocytes</u>						
Unexposed	1.00			<u>Platelets</u>		
<1.3 ppm	0.87	0.75-1.01	0.997	*0.85	0.75-0.96	0.674
≥1.3 ppm	0.88	0.75-1.03		0.91	0.80-1.03	

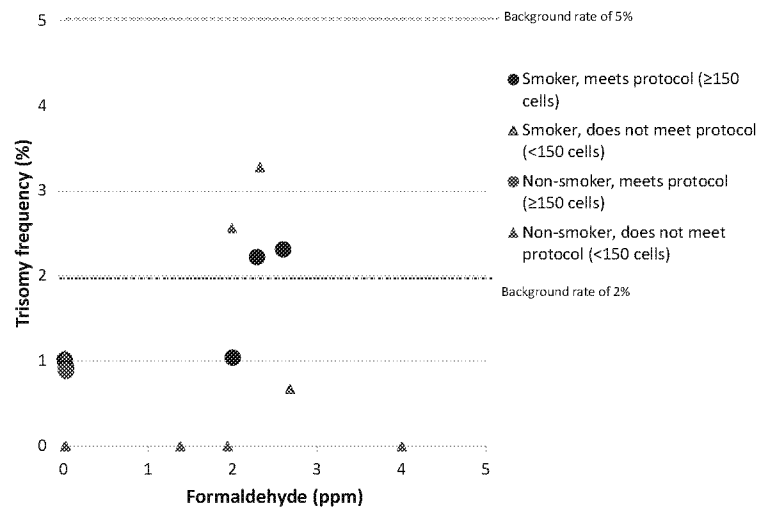
†Comparison between exposed categories

*p<0.05 compared with unexposed

Monosomy 7 – only colored circles met their own internal study protocol



Trisomy 8 - only colored circles met their own internal study protocol

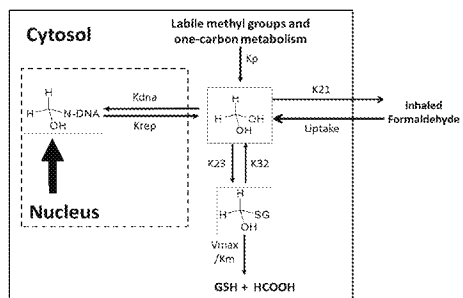


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Epidemiological Conclusions

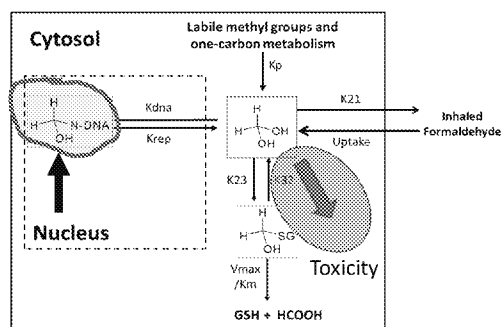
- Epidemiological evaluation of the one cluster of NPC deaths not clearly associated with formaldehyde exposure. Nasal/sino-nasal cancers seemed plausible based on animal studies but increased risk of these tumors has not been seen in the epidemiological studies.
- Conclusions relied upon from Beane Freeman et al. 2010, i.e., association between ML and 'peak' exposure were not verified upon more complete analysis:
 - No excess of ML or AML observed; and
 - Very few decedents with AML had any peak exposure (only 1 within usual latency period).
- Conclusions relied upon from Zhang et al. 2010 inconsistent with fuller analysis of study data, including unreported individual exposure measurements: no associations with exposure level seen among exposed.
- **Weight of evidence synthesis of epidemiological evidence provides very little support for a causal association between formaldehyde and either NPC or AML.**

III. Integrating studies into a more quantitative risk evaluation



Background: Formaldehyde flux, primarily from tissue to air, with significant background levels of various formaldehyde reaction products

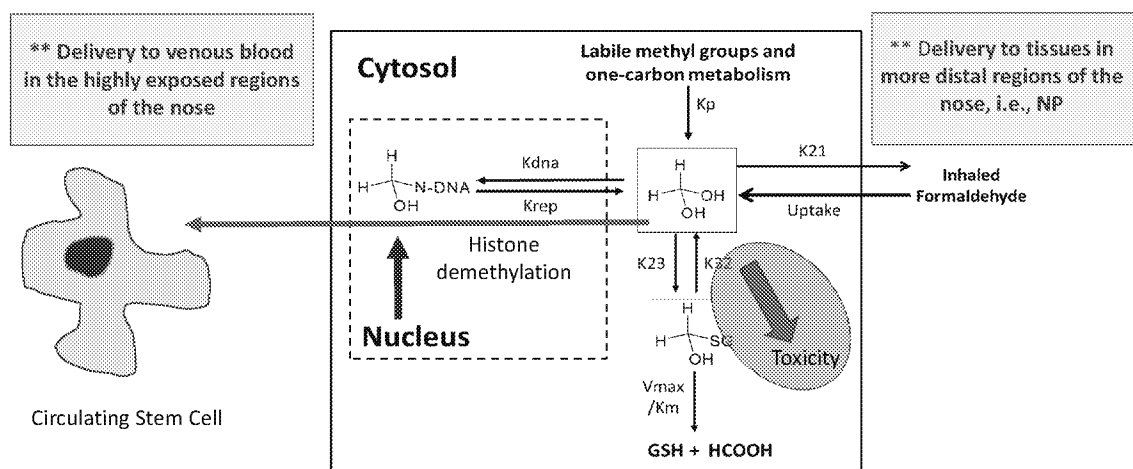
Exposed: Formaldehyde flux, primarily from air to tissue, increases tissue concentration leading to cytotoxicity and increased level of DNA-reaction products



Recommendations/Conclusions: Mode of Action

- ❖ The risk assessment for formaldehyde should be structured around a MOA framework based on the extensive understanding of cancer causation in the rat nose
- ❖ Measures of DNA-reaction products from formaldehyde should be central considerations in evaluating the ability of inhaled formaldehyde to reach other tissues
- ❖ The BBDR model for formaldehyde by Conolly and others could be updated to assist in answering questions about the relative roles of cytotoxicity and DNA-reactivity in cancer in the rat

What would be the proposed MOA for human cancer in light of central role of high doses and cytotoxicity?



** Dosimetry studies indicate that it is unlikely that high tissue concentrations can be achieved in any of these more remote tissues.

Recommendations/Conclusions: NP Cancer Epidemiology

- ❖ The association of NPC with formaldehyde exposure needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde and the presence of relatively high concentrations in all cells.
- ❖ Review experience with other human nasal carcinogens to determine whether there are reasons to expect differential sensitivity in particular portions of the human nose compared to the rat.

Recommendations/Conclusions: LHP Cancer Epidemiology

- ❖ The association of LHP cancer also needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde adding to an already substantial level of cellular formaldehyde.
- ❖ Evaluate experience with other compounds producing leukemia, such as benzene and chemotherapeutic compounds, where bone marrow toxicity is also evident.

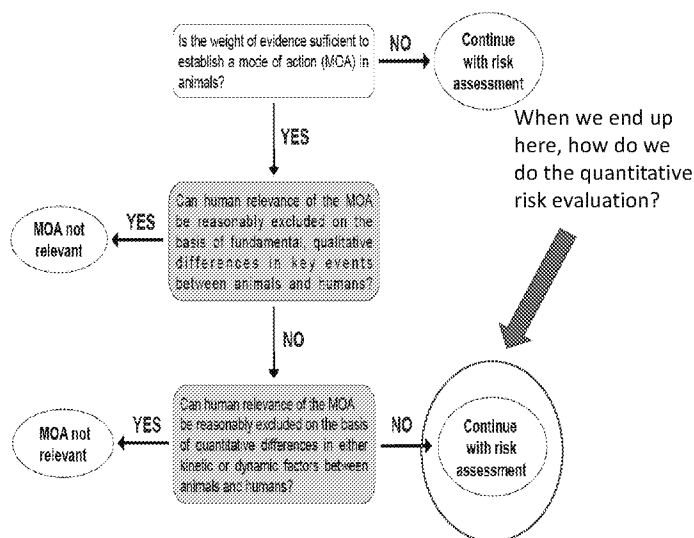
Systematic review is more than just assessing modes-of-action

THE IPCS CONCEPTUAL MOA FRAMEWORK FOR EVALUATING ANIMAL CARCINOGENESIS:

Introduction to the Framework Analysis

- Postulated mode of action (theory of the case)
- Key events
- Concordance of dose-response relationships
- Temporal association
- Strength, consistency and specificity of association of tumour response with key events
- Biological plausibility and coherence
- Other modes of action
- Uncertainties, Inconsistencies, and Data Gaps
- Assessment of postulated mode of action

IPCS general scheme illustrating the main steps in evaluating the human relevance of an animal MOA for tumour formation.



Recommendations/Conclusions: The Integrated Risk Evaluation:

- ❖ The risk assessment should take into account the weight of evidence for causation of a response by formaldehyde, the concentrations in air and tissues associated with these effects, and the overall evidence for particular modes of action.
- ❖ Systematic review needs to evaluate both the qualitative evidence for various MOAs and the manner in which the studies are brought together to support extrapolation models – threshold or low-dose linear - in the quantitative risk assessment.
- ❖ This type of robust evaluation appears beyond the scope of present systematic reviews that focus on toxicity rather than the support for extrapolation models based on mode of action studies.

The participants

Some recent references

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